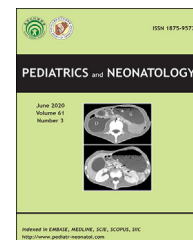




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Perspectives

Interleukin-6 levels in children developing SARS-CoV-2 infection

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Since the declaration of the coronavirus disease 2019 (COVID-19) pandemic status, the total number of cases developing severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has reached 1,696,588 worldwide, with a mortality rate of 6.24%.¹ Interestingly, reports have shown that, compared to adults, the pediatric populations have lower infection rates, less severe clinical presentation with lower likelihood of progression, and more favorable prognosis.² However, the mechanism behind this phenomenon remains elusive. Recently, we demonstrated that COVID-19 severity in adult patients was strongly associated with higher interleukin-6 (IL-6) levels.³ Thus, in this article, we aimed to evaluate the current evidence regarding IL-6 levels in pediatric COVID-19 cases.

Records, dated up to April 5th, 2020, were identified through electronic databases with search terms such as "COVID-19," "SARS-CoV-2," "IL-6," "pediatrics," "neonates," "infants," "children," and "adolescents." No language restrictions were applied. We synthesized the data from seven studies with a total sample size of $n = 127$ pediatric patients, with ages ranging from newborn to adolescence.^{4–10} Subsequently, one study was excluded¹⁰

due to samples testing negative for SARS-CoV-2. The final sample yielded a size of $n = 117$, with slightly higher infection rates among males (59.8%), which is consistent with previous reports.⁵

In contrast to our previous result in adults,³ we observed that pediatric COVID-19 cases had IL-6 levels within normal range (mean: 86.3%; range from 67 to 100%) (Table 1) and that all of the current studies observed patients having mild symptoms. To illustrate, a study with a representative population range of three days to 16 years of age⁵ found an overall mild clinical presentation among cases and increased IL-6 levels were only observed in 17.14% of the total population. In line with this finding, the tendency of mild clinical presentation in children has likewise been recognized in a large epidemiologic study of 2163 children in China¹¹, among which only 0.6% progressed into severe disease.

This finding reinforces previous notions that the cytokine storm, indicated by excessive circulating IL-6, is a possible mechanism of COVID-19 progression³ and that this aggressive inflammatory cascade is less likely to occur in children. The findings also emphasize that IL-6 better reflects the severity of COVID-19 clinical presentation and is relatively more consistent compared to other inflammatory markers such as C-reactive protein (CRP).¹²

Several factors may contribute to the milder presentation observed in children in regard to the immunopathogenic response. The less mature immune system of children

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Table 1 Characteristic of included studies.

Characteristics	Zhang et al. ⁴	Yu et al. ⁵	Du et al. ⁶	Sun et al. ⁷	Su et al. ⁸	Zeng et al. ⁹
Location	China	China	China	China	China	China
Number of cases	3	82	14	8	9	1
Age	6–9 years	3 days - 16 years	6.20 (median)	2 mo - 15 years	11 mo - 9 years	2 weeks (neonates)
Males, %	100	62.2	42.9	75	33.3	100
Major clinical feature	Mild	Mild	Mild-intermediate	Mild	Asymptomatic - mild	Mild
IL-6	67% ↔	82.86% ↔	92.85% ↔	75% ↔	100% ↔	↔

↔ value within the normal reference range.

may result in the lower capability to elicit cytokine release against viral infection, relative to the more mature and vigorous immune responses observed in adults. Other possible explanations include healthier respiratory tracts and less pre-existing damage in children compared to adults.

There are several limitations identified in this current analysis. Only a few studies reported the IL-6 level in COVID-19-infected pediatric patient, with some variations on the IL-6 reference ranges between studies. Thus, further studies with larger sample size and homogenous or standardized measurement are needed to confirm these findings. Additionally, more studies need to focus on the neonate age group, as data regarding clinical presentation of COVID-19 in this highly susceptible age group remains scant. In summary, these findings confirm that IL-6 reflect presence of marked inflammation and severe COVID-19. Based on current evidence, IL-6 levels of children with SARS-CoV-2 infection tend to be within normal range, which reflects the mild nature of clinical presentation in the pediatric population.

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Declaration of Competing Interest

None to declare.

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